

Claims

1. A method for making composite active particles for use in a pharmaceutical composition for pulmonary inhalation, the method comprising jet milling active
5 particles in the presence of particles of additive material and, optionally, air or a compressible gas or fluid.
2. A method as claimed in claim 1, wherein the additive material comprises an amino acid, a metal stearate or a phospholipid.
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3. A method as claimed in claim 2, wherein the additive material comprises one or more of leucine, isoleucine, lysine, valine, methionine, phenylalanine.
4. A method as claimed in claim 3, wherein the additive material comprises
15 leucine and preferably L-leucine.
5. A method as claimed in claim 2, wherein the additive material comprises magnesium stearate.
- 20 6. A method as claimed in claim 2, wherein the additive material comprises lecithin.
7. A method as claimed in any one of the preceding claims, wherein the jet milling is carried out at an inlet pressure of between 0.1 and 3 bar.
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8. A method as claimed in any one of claims 1-6, wherein the jet milling is carried out at an inlet pressure of between 3 and 12 bar.
9. A method as claimed in any one of the preceding claims, wherein at least
30 90% by volume of the active particles are less than 20µm in diameter prior to jet milling.

10. A method as claimed in any one of the preceding claims, wherein at least 90% by volume of the additive particles are less than 20 μ m in diameter prior to jet milling.
- 5 11. A method as claimed in any one of the preceding claims, wherein jet milling is carried out at temperatures below room temperature.
12. A method as claimed in claim 11, wherein jet milling is carried out at a temperature below 10°C and preferably below 0°C.
- 10 13. A method as claimed in any one of the preceding claims, wherein carrier particles are also jet milled with the active particles and the particles of additive material.
- 15 14. A method as claimed in claim 13, wherein the carrier particles have a particle size of at least 20 μ m.
15. A method as claimed in claim 13, wherein the carrier particles have a particle size of less than 30 μ m, preferably less than 20 μ m and more preferably less than 10 μ m.
- 20 16. Composite active particles for use in a pharmaceutical composition made using a method as claimed in any one of the preceding claims.
- 25 17. Composite active particles as claimed in claim 16, for pulmonary inhalation.
18. Composite active particles as claimed in either of claims 16 and 17, wherein the additive material forms a coating on the surface of the additive particles.
- 30 19. Composite active particles as claimed in claim 18, wherein the coating is a discontinuous coating.

20. Composite active particles as claimed in either of claims 18 and 19, wherein the coating of additive material is not more than $1\mu\text{m}$ in thickness.
21. Composite active particles as claimed in any one of claims 16-20, having an
5 MMAD of not more than $10\mu\text{m}$.
22. Composite active particles as claimed in claim 21, having an MMAD of not more than $5\mu\text{m}$, not more than $3\mu\text{m}$, not more than $2\mu\text{m}$, or not more than $1\mu\text{m}$.
- 10 23. Composite active particles as claimed in any one of claims 16-22, wherein at least 90% by weight of the composite active particles have a diameter of not more than $10\mu\text{m}$.
24. Composite active particles as claimed in claim 23, wherein at least 90% by
15 weight of the particles have a diameter of not more than $5\mu\text{m}$, not more than $3\mu\text{m}$, or not more than $1\mu\text{m}$.
25. A pharmaceutical composition comprising composite active particles as claimed in any one of claims 16-24.
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26. A composition as claimed in claim 25, wherein the composition is for pulmonary inhalation.
27. A composition as claimed in either of claims 25 and 26, wherein the
25 composition is a dry powder composition.
28. A composition as claimed in claim 27, wherein the composition further comprises carrier particles.
- 30 29. A composition as claimed in any one of claims 25-28, wherein the composition has a FPF(ED) of at least 70%.

30. A composition as claimed in claim 29, wherein the FPF(ED) is at least 80%, at least 85%, or at least 90%.

31. A composition as claimed in any one of claims 25-28, wherein the
5 composition has a FPF(MD) of at least 60%.

32. A composition as claimed in claim 29, wherein the FPF(MD) is at least 70%, at least 80%, or at least 85%.

10 33. A dry powder inhaler containing a composition as claimed in any one of claims 25-32.

34. Use of an additive material as a milling aid in the jet milling of an active material.

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